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GROUP 120

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
In re Patent Application

Bernauer et al.

Group: 126

Examiner: Reamer, J.

Serial No. 07/686,210, filed April 16, 1991

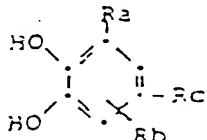
For: CATECHOL DERIVATIVES

INFORMATION DISCLOSURE STATEMENTNutley, New Jersey 07110  
July 22, 1991Honorable Commissioner of Patents and Trademarks  
Washington D.C. 20231

Sir:

This statement is submitted pursuant to and in compliance with the provisions of 1.56, 1.97 and 1.98 of Title 37 of the Federal Regulations, as amended.

The claimed invention relates to a compound of the formula



Ia

wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc is halogen, nitro, cyano or the group  $-(A)_n-(Q)_m-R'$  or  $-(A)_n-Q-R^2$ , A is vinylene optionally substituted by lower alkyl, n is the integer 0 or 1, m is the integer 0 or 1, R' is the group  $-COR^3$ , an aromatic carbocyclic group, or an aromatic or partially unsaturated heterocyclic group attached

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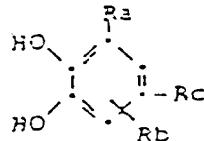
July 22, 1991

Ellen C. Colath

via a carbon atom, R<sup>2</sup> is hydrogen or an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue, R<sup>3</sup> is hydroxy, amino, an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue attached via an oxygen atom or an imino or lower alkylimino group or a saturated, N-containing heterocyclic group attached via a ring nitrogen atom, Q is the group -CO- or >C=N(Z)<sub>p</sub>-R<sup>4</sup>, Z is an oxygen atom or an imino group, p is the integer 0 or 1 and R<sup>4</sup> is hydrogen or a saturated or partially unsaturated lower hydrocarbon residue which is optionally substituted and which is optionally attached via a carbonyl group,

or an ester or ether derivative thereof which is hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof.

In another aspect, the invention relates to pharmaceutical compositions comprising a compound of the formula



Ia

wherein Ra is nitro or cyano, Rb is hydrogen or halogen, Rc is halogen, nitro, cyano or the group -(A)<sub>n</sub>-(Q)<sub>m</sub>-R' or -(A)<sub>n</sub>-Q-R<sup>2</sup>, A is vinylene optionally substituted by lower alkyl, n is the integer 0 or 1, m is the integer 0 or 1, R' is the group -COR<sup>3</sup>,

an aromatic carbocyclic group, or an aromatic or partially unsaturated heterocyclic group attached via a carbon atom, R<sup>2</sup> is hydrogen or an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue, R<sup>3</sup> is hydroxy, amino, an optionally substituted, saturated or partially unsaturated lower hydrocarbon residue attached via an oxygen atom or an imino or lower alkylimino group or a saturated, N-containing heterocyclic group attached via a ring nitrogen atom, Q is the group -CO- or >C=N(Z)<sub>p</sub>-R<sup>4</sup>, Z is an oxygen atom or an imino group, p is the integer 0 or 1 and R<sup>4</sup> is hydrogen or a saturated or partially unsaturated lower hydrocarbon residue which is optionally substituted and which is optionally attached via a carbonyl group,  
or an ester or ether derivative thereof which is hydrolyzable under physiological conditions or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier material.

In connection with the foregoing invention, applicants wish to bring the following publications to the attention of the Patent and Trademark Office.

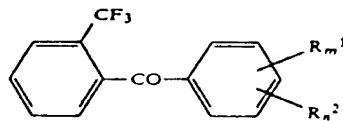
1. Kitahara, et al., U.S. Patent 4,622,066, November 11, 1986;
2. GB 967605, August 26, 1964;
3. Miyamoto et al., Chemical Abstracts, Vol. 99, 121998 (1983);
4. EP 79141, October 1982;
5. Backstrom et al., U.S. 4,963,590, October 16, 1990,

filed November 27, 1987; corresponding to New Zealand  
222 729;

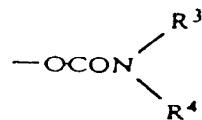
6. Hamazaki et al., U.S. Patent 4,124,726,  
November 7, 1987;
7. Gapinski, U.S. Patent 4,801,616, January 31, 1989;
8. Johnson et al., U.S. Patent 3,985,783, October 12, 1976;
9. Chemical Abstracts, Vol. 95, 135254t (1981);
10. British Patent Publication No. 2,038,819;
11. Nikadejevic, et al., Catechol-O-Methyl Transferase II. A  
New Class of Inhibitors of Catechol-O-Methyl  
Transferase, J. Pharmacol. Exp. Ther. 174, 83-93 (1970);
12. Fahn et al., Effect of Catechol-O-Methyl Transferase  
Inhibitor, U-0521 with Levodopa Administration, Biochem.  
Pharmacol. 28, 1221-1225 (1979);
13. Reches et al., Catechol-O-Methyl Transferase Inhibition  
by U-0521 Increase Striatal Utilization of Levodopa,  
Arch. Pharmacol. 320, 34-37 (1982);
14. Borchardt, et al., Catechol-O-Methyl Transferase, J. Med.  
Chem. 25, 258-263 (1982);
15. Borchardt and Huber, Catechol-O-Methyl Transferase, J.  
Med. Chem. 25, 321-323 (1982);
16. Borchardt and Huber, Function and Regulation of Monoamine  
Enzymes, Basic and Clinical Aspects, ed. E. Usdin, N.  
Weinder and M.B.H. Youdim, MacMillan Publishers, 1981,  
657-664;
17. European Patent Publication No. 142,283, May 22, 1985;
18. Chemical Abstracts 92, 146461x (1980);
19. Chemical Abstracts 98, 50111f (1983);
20. Traxler and Ghisalba, A Genetic Approach to the  
Biosynthesis of the Rifamycin-Chromophore in  
Nocardia Mediterranei, J. Antibiotics 35(10),  
1361-6 (1982);

21. Chemical Abstracts Service, Registry Handbook 1965-1971, page 10666R; and
22. Britton et al., U. S. Patent No. 2,199,389, May 7, 1940.

Publication 1) discloses compounds of the formula



wherein  $\text{R}^1$  is a group of the formula:  $-\text{OM}$  (in which  $\text{M}$  is hydrogen or alkali metal), lower alkoxy, lower acyloxy, a group of the formula:

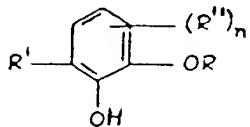


(in which  $\text{R}^3$  and  $\text{R}^4$  are same or different and hydrogen or lower alkyl) or a group of the formula:  $-\text{OCH}_2\text{COOR}^5$  (in which  $\text{R}^5$  is hydrogen, lower alkyl or alkali metal);  $\text{R}^2$  is halogen, nitro, chlorosulfonyl, sulfo, trifluoromethyl or a group of the formula:  $-\text{SCF}_2\text{H}$ ; and  $\text{m}$  and  $\text{n}$ , are each an integer of 1 to 4 provided that the sum of  $\text{m}$  and  $\text{n}$  is not more than 5.

With the aid of applicants' disclosure, Publication 1) arguably generically discloses a compound of formula I wherein Ra is nitro, Rb is hydrogen and Rc is 2-(trifluoromethyl) benzoyl which is stated to have selective herbicidal activity

on grasses, not crops.

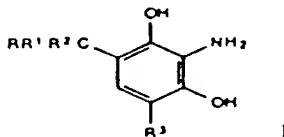
Publication 2) relates to a process for the production of orthodihydroxy benzene derivatives of the formula



where R represents a hydrogen atom,  $R'$  represents a hydrogen or halogen atom or an alkyl, alkenyl or alkoxy radical of from 1 to 4 carbon atoms,  $R''$  represents a halogen atom or a nitro, sulpho, sulphino, mercapto or hydroxyl group or a hydrocarbon or oxygenated hydrocarbon group containing from 1 to 18 carbon atoms, or an amino methyl, sulphino methyl, mercapto methyl or sulphonyl methyl group and n is 0 or an integer from 1 to 3.

Publication 2) arguably generically discloses a compound of formula I of the invention wherein Ra is nitro, Rc is nitro or halogen and Rb is hydrogen.

Publication 3) discloses compounds of the formula

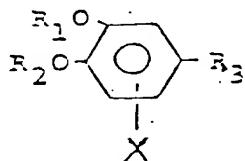


R=alkyl, (un)substituted Ph, aralkyl; R<sup>1</sup>=H, R<sup>2</sup>=OH, alkoxy; R<sup>1</sup>R<sup>2</sup>=O; R<sup>3</sup>=H, halogen, alkyl, SPh, which inhibit 5-lipoxygenase.

In addition, Publication 3) discloses the intermediate compound, 2,4,3-(HO)<sub>2</sub>(O<sub>2</sub>N)C<sub>6</sub>H<sub>2</sub>COPh, which arguably are "positional isomers" of the claimed compounds.

Publication 4), referred to in Publication 3), discloses pharmaceutical compositions for treating bronchial or lung and tracheal allergic diseases and inflammations induced by prostaglandin comprising a compound of formula I above.

Publication 5) discloses allegedly pharmacologically active catechol derivatives of the formula



wherein R<sub>1</sub> and R<sub>2</sub> independently represent hydrogen, alkyl, acyl or optionally substituted aroyl, lower alkylsulphonyl or alkylcarbamoyl or taken together form a lower alkylidene or cycloalkylidene group; X represents halogen, nitro, cyano, lower alkylsulphonyl, sulphonamido, aldehyde, carboxyl or trifluoromethyl in position 5 or 6 and R<sub>3</sub> represents hydrogen, halogen, hydroxyalkyl, amino, nitro, cyano, trifluoromethyl, lower alkylsulfonyl, sulfonamide, aldehyde, alkylcarbonyl, aralkylidonecarbonyl or carboxyl or a group selected from -CH=C(R<sub>4</sub>)R<sub>5</sub> and -CH<sub>2</sub>CH(R<sub>4</sub>)R<sub>5</sub> wherein R<sub>4</sub>

represents hydrogen, alkyl, cyano, carboxyl or acyl and R<sub>5</sub> represents hydrogen, cyano, carboxyl, alkoxy carbonyl, carboxy alkenyl, nitro, acyl, hydroxy alkyl, carboxy alkyl or one of the optionally substituted groups; aroyl or heteroaroyl; or R<sub>4</sub> and R<sub>5</sub> together form a five to seven membered, optionally substituted cycloalkanone ring; -(CO)<sub>n</sub>(CH<sub>2</sub>)<sub>m</sub>-COR, wherein n is 0 or 1, and m is 0-7 and R represents hydroxy, alkyl, carboxy alkyl, optionally substituted alkene, alkoxy or optionally substituted amino; -CON(R<sub>8</sub>)R<sub>9</sub> wherein R<sub>8</sub> and R<sub>9</sub> independently represent hydrogen or one of the following optionally substituted groups; alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, or together form an optionally substituted piperidyl group; and -NH-CO-R<sub>10</sub> wherein R<sub>10</sub> represents a substituted alkyl group.

In another aspect, publication 5) discloses pharmaceutical compositions and methods for inhibiting catechol-O-methyl transferase and for treating Parkinson's disease, heart failure, depression and hypertension comprising a compound of formula I.

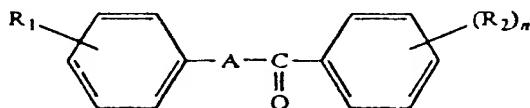
While this publication may be pertinent to the claimed invention and the Examiner may wish to consider it, the publication is not available as a prior art reference against the instant application. As is evident, the filing date of US 4,963,590, is antedated by the filing date of applicants' U.S. priority application, Serial No. 07/022,891, namely, March 6, 1987.

Applicants are not aware of any foreign patents

corresponding to U.S. 4,963,590, that issued prior to the filing date of applicants' U.S. priority application.

Furthermore, U.S. 4,963,590 does not claim subject matter which overlaps with that of the instant application.

Publication 6) relates to compounds of the formula

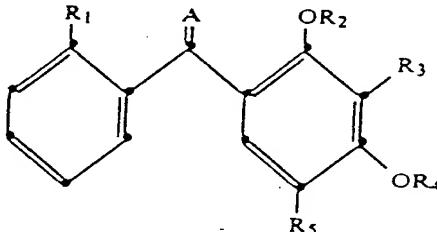


wherein R<sub>1</sub> represents hydrogen, halogen, hydroxy, C<sub>1-8</sub> alkyl or C<sub>1-8</sub> alkoxy,

R<sub>2</sub> represents hydrogen, halogen, hydroxy, vinyl, C<sub>1-8</sub> alkyl or C<sub>1-8</sub> alkoxy,

A represents carbonyl, methylene or a single bond, and n is an integer of 1 to 4.

Publication 7) discloses diphenylmethane compounds of the formula



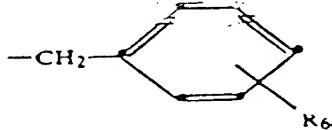
and pharmaceutically acceptable salts thereof wherein R<sub>1</sub> is -OH, -O-(C<sub>1-C<sub>4</sub></sub> alkyl), halo, or -OCO(C<sub>1-C<sub>4</sub></sub> alkyl);

A is O, CH<sub>2</sub>, or CH(C<sub>1-C<sub>4</sub></sub> alkyl);

R<sub>2</sub> is hydrogen or C<sub>1-C<sub>4</sub></sub> alkyl;

R<sub>3</sub> is C<sub>1-C<sub>4</sub></sub> alkyl or C<sub>2-C<sub>4</sub></sub> alkenyl;

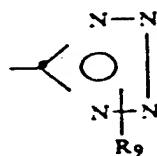
R<sub>4</sub> is -H, C<sub>1-C<sub>4</sub></sub> alkyl, -CO(C<sub>1-C<sub>4</sub></sub> alkyl) -alk-R<sub>6</sub>, or



or R<sub>3</sub> and R<sub>4</sub> when taken with the oxygen atom to which R<sub>4</sub> is attached are -CH<sub>2</sub>CH(CH<sub>3</sub>)O-;

R<sub>5</sub> is -H or C<sub>1-C<sub>4</sub></sub> alkyl; and

R<sub>6</sub> is -CN, -COOH, -COO(C<sub>1-C<sub>4</sub></sub> alkyl), -CONR<sub>7</sub>R<sub>8</sub>, or

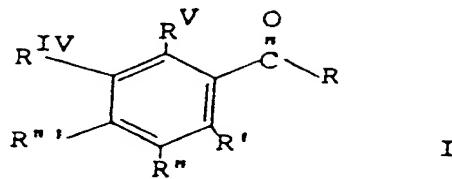


where

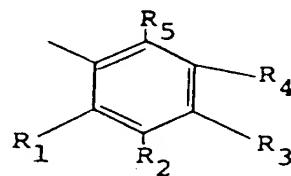
R<sub>7</sub> and R<sub>8</sub> are each independently hydrogen or C<sub>1-C<sub>3</sub></sub> alkyl,

R<sub>9</sub> is hydrogen or C<sub>1-C<sub>4</sub></sub> alkyl, and "alk" is a divalent organic radical derived from a C<sub>1-C<sub>8</sub></sub> aliphatic hydrocarbon.

Publication 8) relates to a process for ring acylation of phenols to obtain compounds of the formula



wherein R', R'', R''', R'''' and R<sup>IV</sup> are independently selected from the group consisting of hydrogen, hydroxy, (C<sub>1-3</sub>)-alkyl, (C<sub>1-3</sub>)-alkoxy and carbo-(C<sub>1-3</sub>)-alkoxy, with the proviso that at least one of R' and R''' is hydroxy; R is a (C<sub>1-3</sub>)-alkyl radical or the group



wherein the substituents R<sub>1</sub> through R<sub>5</sub> are independently selected from hydrogen, (C<sub>1-3</sub>)-alkyl, (C<sub>1-3</sub>)-alkoxy, benzyloxy, hydroxy, halo, nitro, cyano and amino.

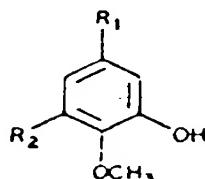
Publications 9) and 10) disclose 3,5-dinitro-1,2-dihydroxybenzene.

Publication 11) relates to, for example, 3-methoxy-4,5-dihydroxybenzoic acid and the like (see pages 87-88).

Publication 12) relates to a study of the effect of 3',4'-dihydroxy-2-methyl-propiophenone, a catechol-O-methyl transferase inhibitor (COMT), with levodopa administration.

Publication 13) relates to a study of the effect of COMT inhibition by 3',4'-dihydroxy-2-methyl propiophenone on Dopa metabolism in rat striatum.

Publication 14) relates to a study of 5-substituted-3-hydroxy-4-methoxybenzoic acids and 5-substituted-3-hydroxy-4-methoxybenzaldehydes of the formulas



	R <sub>1</sub>	R <sub>2</sub>	R <sub>1</sub>	R <sub>2</sub>
1	CO <sub>2</sub> H	H	10	CHO
2	CO <sub>2</sub> H	OCH <sub>3</sub>	11	CHO
3	CO <sub>2</sub> H	Cl	12	CHO
4	CO <sub>2</sub> H	Br	13	CHO
5	CO <sub>2</sub> H	I	14	CHO
6	CO <sub>2</sub> H	NO <sub>2</sub>	15	CHO
7	CO <sub>2</sub> H	NH <sub>2</sub>	16	CHO
8	CO <sub>2</sub> H	N(CH <sub>3</sub> ) <sub>2</sub>	17	CHO
9	CO <sub>2</sub> H	CN		SC(S)OEt

as potential inhibitors of COMT.

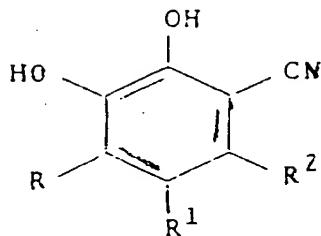
Publication 15) relates, for example, to 5-hydroxy-3-mercaptop-4-methoxybenzoic acid.

Publication 16) discloses 3-substituted-4-methoxy-5-hydroxybenzoic acid. The substituents may be, for example, OCH<sub>3</sub>, Cl, Br, I, NO<sub>2</sub>, NH<sub>2</sub>, N(CH<sub>3</sub>)<sub>2</sub>, CN, SH. Also disclosed are 3-substituted-4-methoxy-5-hydroxybenzaldehyde, the substituents may be, for example, F, Cl, Br, I, NO<sub>2</sub>, OH,



Publication 17) describes phenylethylamines, having, for example, hydroxy, halogen and nitro substituents.

Publication 18) discloses 3-cyanocatechol derivatives of the formula

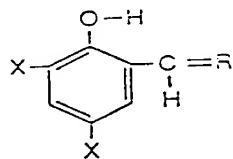


wherein R, R<sup>1</sup> and R<sup>2</sup> can be, for example, H,H,H; H,MeO,H; Me,H,H; Me,Me,H; H, Cl, H; Cl,Cl,H; Br,H,H; H,H,I.

Publications 19) and 20) disclose, among others, the compounds 3-nitro-4,5-dihydroxybenzoic acid and 3-amino-4,5-dihydroxybenzoic acid.

Publication 21) discloses, among others, the compound 5-formyl-2,3-dihydroxybenzonitrile.

Publication 22) discloses compounds of the formula



wherein one X is a nitro group, the other X is hydrogen or a nitro group, and R is an organic residue containing a double bond in conjugated relationship to that existing between R and the

side-chain carbon atom attached to the benzene nucleus.

The Examiner is respectfully requested to consider the above publications in connection with the examination of the captioned application.

The Examiner is hereby authorized to call the undersigned attorney of record "collect" on any matter connected with this application. The telephone number is Area Code (201) 235-5171. In the absence of the undersigned attorney of record, the call will be accepted by another attorney empowered in this application.

Respectfully submitted,

  
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